July 30, 1987

Serial No. 7-030658 Docket No. 7025 By JMM
Application of Edward Davison et al. Filed: March 25, 1987
Entitled: PHARMACEUTICALLY ACCEPTABLE SALTS

The following, due ..... in the U.S. Patent Office, has been received there on the date stamped hereon:

- ☐ Affidavit ☐ Declaration
- ☐ Amendment
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- ☐ Deposit Account Order Form
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- ☐ Issue Fee Transmittal
- ☐ Letter
- ☐ Notice of Appeal
- ☐ Oath or ☐ Declaration
- ☐ Power of Attorney
- ☐ Priority Document
- ☐ Specification
- ☐ Claims
- ☐ Disclosure Statement
- ☒ Preliminary Communication

J. R. Reuss

SPC 7025/JMM

PATENT

#3
EBW
8-14-87

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

EDWARD DAVISON ET AL.	:	GROUP ART UNIT: 125
SERIAL NO.: 7-030658	:	
FILED: MARCH 25, 1987	:	
FOR: PHARMACEUTICALLY ACCEPTABLE SALTS	:	

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Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Preliminary Communication

Attached is a certified copy of U.K. Application 8,608,335, filed April 4, 1986, from which the present U.S. application claims priority. This certified copy was not available at the time the present application was filed.

Respectfully submitted,

James M. McManus
Reg. No. 28,642
Agent for Applicants
Tel.: (203) 441-4903

Attachment
Date: July 30, 1987

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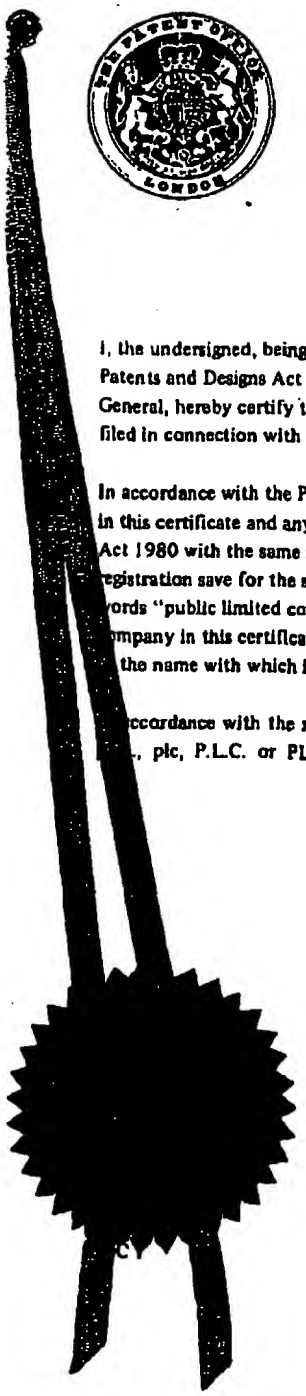

THE PATENT OFFICE
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In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents, has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or the inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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PATENTS ACT 1977

4 APRIL 1986

PATENTS FORM No. 1/77 (Revised 1982)
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07/04/86 83213 PAT### 10.00

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The Patent Office
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London, WC2A 1AY

1986
0 8 3 3 5

REQUEST FOR GRANT OF A PATENT

8608335

THE GRANT OF A PATENT IS REQUESTED BY THE UNDERSIGNED ON THE BASIS OF THE PRESENT APPLICATION

I Applicant's or Agent's Reference *(Please insert if available)* PLC 423

II Title of Invention
Improvements in Pharmaceutically Acceptable Salts

III Applicant or Applicants *(See note 2)*
Name (First or only applicant) Pfizer Limited
Country United Kingdom State ADP Code No.
Address Ramsgate Road,
Sandwich, Kent. CT13 9NJ
Name (of second applicant, if more than one)
Country State
Address

IV Inventor (see note 3)
(a) The applicant(s) is/are the sole/joint inventor(s)
or
(b) A statement on Patents Form No 7/77 is/will be furnished

V Name of Agent (if any) *(See note 4)* Dr. J.W. Moore ADP CODE NO

VI Address for Service (See note 5)
Pfizer Limited, Ramsgate Road, Sandwich, Kent. CT13 9NJ

VII Declaration of Priority (See note 6)

Country	Filing date	File number

VIII The Application claims an earlier date under Section 8(3), 12(6), 15(4), or 37(4) (See note 7)
Earlier application or patent number and filing date

P0093812

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IX Check List *(To be filled in by applicant or agent)*

A	The application contains the following number of sheet(s)		B	The application as filed is accompanied by:-	
1	Request	1 Sheet(s)	1	Priority document	-
2	Description	11 Sheet(s)	2	Translation of priority document	-
3	Claim(s)	- Sheet(s)	3	Request for Search	-
4	Drawing(s)	- Sheet(s)	4	Statement of Inventorship and Right to Grant	-
5	Abstract	- Sheet(s)			

X It is suggested that Figure No ..... of the drawings (if any) should accompany the abstract when published.

XI Signature *(See note 8)* J.W. Moore

NOTES:

1. This form, when completed, should be brought or sent to the Patent Office together with the prescribed fee and two copies of the description of the invention, and of any drawings.
2. Enter the name and address of each applicant. Names of individuals should be indicated in full and the surname or family name should be underlined. The names of all partners in a firm must be given in full. Bodies corporate should be designated by their corporate name and the country of incorporation and, where appropriate, the state of incorporation within that country should be entered where provided. Full corporate details, eg "a corporation organised and existing under the laws of the State of Delaware, United States of America," trading styles, eg "trading as xyz company", nationality, and former names, eg "formerly (known as) ABC Ltd." are not required and should not be given. Also enter applicant(s) ADP Code No. (if known).
3. Where the applicant or applicants is/are the sole inventor or the joint inventors, the declaration (a) to that effect at IV should be completed, and the alternative statement (b) deleted. If, however, this is not the case the declaration (a) should be struck out and a statement will then be required to be filed upon Patent Form No 7/77.
4. If the applicant has appointed an agent to act on his behalf, the agent's name and the address of his place of business should be indicated in the spaces available at V and VI. Also insert agent's ADP Code No. (if known) in the box provided.
5. An address for service in the United Kingdom to which all documents may be sent must be stated at VI. It is recommended that a telephone number be provided if an agent is not appointed.
6. The declaration of priority at VII should state the date of the previous filing and the country in which it was made and indicate the file number, if available.
7. When an application is made by virtue of section 8(3), 12(6), 15(4), or 37(4) the appropriate section should be identified at VIII and the number of the earlier application or any patent granted thereon identified.
8. Attention is directed to rules 90 and 108 of the Patent Rules 1982.
9. Attention of applicants is drawn to the desirability of avoiding publication of inventions relating to any article, material or device intended or adapted for use in war (Official Secrets Acts, 1911 and 1920). In addition after an application for a patent has been filed at the Patent Office the comptroller will consider whether publication or communication of the invention should be prohibited or restricted under section 22 of the Act and will inform the applicant if such prohibition is necessary.
10. Applicants resident in the United Kingdom are also reminded that, under the provisions of section 23 applications may not be filed abroad without written permission or unless an application has been filed not less than six weeks previously in the United Kingdom for a patent for the same invention and no direction prohibiting publication or communication has been given or any such direction has been received.

P0093813

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PATENT SPECIFICATION

PATENTS ACT 1977

Pfizer Limited,
Sandwich, Kent.

PLC 423

P0093814

DESCRIPTION

Improvements in Pharmaceutically Acceptable Salts

The present invention relates to improved pharmaceutical salts of amlodipine and pharmaceutical compositions thereof.

The compound amlodipine (3-ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate) is a potent and long acting calcium channel blocker having utility as an anti-ischaemic and anti-hypertensive agent.

European patent application publication no. 89167 discloses several different pharmaceutically acceptable salt forms of amlodipine. In particular the pharmaceutically acceptable acid addition salts are said to be those formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions such as the hydrochloride, hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate salts. Of these salts the maleate is disclosed as being particularly preferred.

It has now unexpectedly been found that the benzene sulphonate salt (hereinafter referred to as the besylate salt) has a number of advantages over the known salts of amlodipine and, additionally has unexpectedly been found to have a unique combination of good formulation properties which make it particularly suitable for the preparation of pharmaceutical formulations of amlodipine.

Thus according to the present invention there is provided the besylate salt of amlodipine.

In a further aspect the invention provides a pharmaceutical composition of the besylate salt of amlodipine together with a pharmaceutically acceptable diluent or carrier.

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The invention further provides a tablet formulation comprising the besylate salt of amlodipine in admixture with excipients. A preferred formulation includes the besylate salt, a compression aid such as microcrystalline cellulose, an additive to provide sheen to the tablet such as anhydrous dibasic calcium phosphate, a disintegrant such as sodium starch glycollate and a lubricant such as magnesium stearate.

In addition the invention provides a capsule formulation comprising the besylate salt of amlodipine in admixture with excipients. A preferred formulation includes the besylate salt, an inert diluent, a dried disintegrant and a lubricant as described above.

The invention further provides the besylate salt of amlodipine in sterile aqueous solution for parenteral administration.

The invention also provides the besylate salt of amlodipine for use in treating ischaemic heart disease, especially angina, or hypertension, in a human being.

Although amlodipine is effective as the free base, in practice it is best administered in the form of a salt of a pharmaceutically acceptable acid. In order to be suitable for this purpose the pharmaceutically acceptable salt must satisfy the following four physiochemical criteria:

1. Good solubility;
2. Good stability;
3. Non-hygroscopicity;
4. Processability for tablet formulation, etc.

It has been found that whilst many of the salts outlined above satisfy some of these criteria, none satisfy them all and even the preferred maleate, whilst exhibiting excellent solubility tends to break-down after

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a few weeks. Consequently a range of pharmaceutically acceptable salts of amlodipine has been made and evaluated using these criteria:

1. Generally, it is known in the art that a good aqueous solubility is necessary for good bioavailability. Usually a solubility of greater than 1 mg ml^{-1} at pH 1-7.5 is sought although higher solubilities are required to formulate injections. In addition salts which provide solutions having a pH close to that of blood (7.4) are preferred because they are readily biocompatible and can easily be buffered to the required pH range without altering their solubility.

As can be seen from the following comparative data the besylate salt of amlodipine exhibits good solubility characteristics, compared with other salts.

TABLE 1

Salt	solubility mg ml^{-1}	pH at saturation
Benzene sulphonate (besylate)	4.6	6.6
Toluene sulphonate (tosylate)	0.9	5.9
Methane sulphonate (mesylate)	>25	3.1
Succinate	4.4	4.9
Salicylate	1.0	7.0
Maleate	4.5	4.8
Acetate	50	6.6
Hydrochloride	50	3.5

2. Good stability in the solid state is very important for tablets and capsules, whilst good stability in solution is required for an aqueous injection.

In order to screen for chemical stability, each of the salts was blended in a powder vehicle and formed into tablets or capsules. In the case of tablets the vehicle comprised microcrystalline cellulose in 50:50

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combination with anhydrous dibasic calcium phosphate. In the case of capsules the vehicle comprised mannitol in 4:1 combination with dried maize starch. These were then stored in sealed vials at 50 and 75°C for up to three weeks. The drug and any breakdown products were extracted with methanol:chloroform (50:50) and separated on silica tlc plates using a variety of solvent systems.

The results were compared and the salts ranked according to the number and amount of breakdown products produced.

By comparing the results the following rank order emerges with besylate being the most stable salt and hydrochloride the least stable.

Salt	Stability
Besylate	most stable
Mesylate	↓
Tosylate	↓
Succinate	↓
Salicylate	↓
Maleate	↓
Acetate	↓
Hydrochloride	unstable

3. In order to provide stable formulations it is desirable to have a non-hygroscopic salt. In the solid state where drug content is high, absorbed films of moisture can act as a vector for hydrolysis and chemical breakdown. It is the hygroscopic nature of a drug or its salt which contributes to the free moisture which is normally responsible for instability.

Only the maleate, tosylate and besylate salts do not pick up any moisture when exposed to 75% relative

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humidity at 37°C for 24 hours. Therefore the besylate salt can be considered to be non-hygroscopic and thus provides stable formulations while minimising the risk of intrinsic chemical breakdown.

4. The final characteristic of an acceptable salt to be considered is the processability, i.e. the compression properties and also the ability not to stick or adhere to the tablet making machinery.

For high dose formulations, good compressibility is very important to make elegant tablets. With lower dose tablets the need for good compressibility can be eliminated to a certain extent by the use of suitable diluting excipients called compression aids. Microcrystalline cellulose is a commonly used compression aid. However whatever the dose the adhesion of the drug to the punches of the tablet machine must be avoided. When drug accumulates on the punch surfaces this causes the tablet surface to become pitted and therefore unacceptable. Also sticking of the drug in this way results in high ejection forces when removing the tablet from the machine. In practice it is possible to reduce sticking by wet-massing, careful selection of excipients and the use of high levels of anti-adherents, e.g. magnesium stearate. However selection of a salt with good anti-adhesion properties minimises these problems.

In order to compare the stickiness of the various salts of amlodipine the following procedure was carried out using conventional tablet making machinery: fifty tablets containing calcium sulphate dihydrate, microcrystalline cellulose and amlodipine besylate were made (47.5:47.5:5), the material sticking to the tablet punch was then extracted using methanol and the amount measured spectrometrically. This procedure was then repeated for runs of 100, 150, 200, 250 and 300 tablets. After each run the amount of material sticking to the

P0093819

tablet punch was measured after extraction with methanol. The values are plotted and an average value calculated from the slope of the line produced.

This same procedure was then repeated for each of the salts of amlodipine. The amount of amlodipine measured as sticking to the tablet punch is shown in Table 2 for each salt and relative to the maleate salt.

TABLE 2

Salt	Stickiness	
	μg Amlodipine cm^{-2} tablet^{-1}	Relative to maleate
Mesylate	1.16	58%
Besylate	1.17	59
Tosylate	1.95	98
Maleate	1.98	100
Free base	2.02	102
Succinate	2.39	121
Hydrochloride	2.51	127
Salicylate	2.85	144

Clearly the besylate has superior anti-adhesion properties to the maleate. Whilst the mesylate also shows good processability it tends to be isolated as the anhydride but this equilibrates to the monohydrate leading to variable composition after manufacture which makes it unacceptable for use in tablets.

Thus the besylate salt of amlodipine shows a unique combination of good solubility, good stability, non-hygroscopicity and good processability which makes it outstandingly suitable for the preparation of pharmaceutical formulations of amlodipine.

In order that the present invention be more readily understood, reference is now made to the following Examples.

P0093820

Example 1

Preparation of Besylate salt of Amlodipine

Amlodipine base (65.6g, 0.161 mols) was slurried in industrial methylated spirit (326.4 ml) and cooled to 5°C. Benzenesulphonic acid (26.2g, 0.168 mols) was dissolved in industrial methylated spirit (65.6 ml) at 5°C and added to the slurry of the base. The resulting slurry was then granulated, filtered and washed with 2 volumes of industrial methylated spirit (65.6 ml). The damp solid was slurried at 5°C for 1hr in industrial methylated spirit (327.6 ml), filtered, washed with 2 volumes of industrial methylated spirit (65.6 ml) and dried under vacuum at 55°C for 24 hours. A yield of 76.5g (83.8%) was obtained with the following analysis.

Melting Point 201.0°C.

Analysis %	C	H	N
Calc.	55.07	5.51	4.94
Found	54.91	5.46	4.93

Example 2

Formulation of Tablets Containing Besylate Salt of Amlodipine

Amlodipine besylate was blended with sodium starch glycollate and anhydrous dibasic calcium phosphate for 5 minutes. This mixture was then sieved, reblended and sieved again followed by blending with microcrystalline cellulose. The resultant mixture was then sieved again and blended for a further 10 minutes. Finally magnesium stearate was added and the whole mixture blended for 5 minutes. The blend was then pressed into tablets using conventional tablet making machinery.

This method was used to make tablets containing different concentrations of the amlodipine besylate salt as shown in Table 3.

P0093821

TABLE 3 : TABLET COMPOSITIONS

Besylate salt (mg)	Microcrystalline cellulose (mg)	Anhydrous dibasic calcium (mg)	Sodium starch glycollate (mg)	Magnesium stearate (mg)
1.736	63.514	31.750	2.00	1.00
3.472	62.028	31.500	2.00	1.00
6.944	124.056	63.000	4.00	2.00
13.889	248.111	126.000	8.00	4.00

P0093822

Example 1

Formulation of Capsules Containing Besylate Salt of Amlodipine

Microcrystalline cellulose and dried maize starch were pre blended. The besylate salt of amlodipine was then mixed with some of this preblend and then sieved. The remainder of the preblend was then added and mixed for 10 minutes. This was then sieved again and mixed for a further 5 minutes.

This method was used to make capsules containing different concentrations of the amlodipine besylate salt as shown in Table 4.

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TABLE 4 : CAPSULE COMPOSITIONS

Besylate salt (mg)	Microcrystalline cellulose (mg)	Dried maize starch (mg)	Magnesium stearate (mg)	Total Capsule weight (mg)
1.736	38.014	10.00	0.250	50
3.472	76.028	20.00	0.500	100
6.944	72.556	20.00	0.500	100
13.889	145.111	40.00	1.00	200

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It will be appreciated from the foregoing that what we will claim may include the following:-

1. The besylate salt of amlodipine

2. A pharmaceutical composition of the besylate salt of amlodipine together with a pharmaceutically acceptable diluent or carrier.

3. A tablet formulation comprising the besylate salt of amlodipine in admixture with excipients.

4. A capsule formulation comprising the besylate salt of amlodipine in admixture with excipients.

5. A sterile aqueous solution of the besylate salt of amlodipine.

6. The besylate salt of amlodipine for use in treating ischaemic heart disease, especially angina, or hypertension, in a human being.

7. A method of protecting the heart from the deleterious effects of ischaemia, particularly angina, which comprises administering an effective amount of the besylate salt of amlodipine or pharmaceutical composition as defined above; and

8. A method of treating hypertension which comprises administering an effective amount of the besylate salt of amlodipine or pharmaceutical composition as defined above.

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